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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Dong Jian-yun	§	**ART UNIT: 1648**
	§	
FILED:September 15, 2003	§	**EXAMINER:**
	§	**Humphrey, Louise W.Z.**
SERIAL NO.: 10/663,360	§	
	§	**CONFIRMATION NO.**
FOR: Method of Testing Drug Susceptibility of HIV	§	**1654**
	§	**DOCKET:**
	§	**D6577CIP/D/CIP2**

MS Non-Fee Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313

RESPONSE TO RESTRICTION REQUIREMENT

Dear Sir:

In response to the Examiner communication mailed June 16, 2006, Applicant respectfully note that claims 1 and 44 are both generic. Thus, Applicant hereby provisionally elects the following species with traverse for examination: nucleoside RT inhibitors as anti-HIV agents with regards to claims 1-43 and protease inhibitors as anti-HIV agents with regards to claims 44-58; before the cell culture is contacted with the first HIV sample as the order of addition of anti-HIV agent with regards to claims 1-43; PBMC as the first cell culture with regards to claims 44-58 and human T-lymphoma cell line (HUT78) as the human cell naturally expressing cell surface co-receptors with regards to claims 1-43 and claims 44-58.

The Examiner states that the application contains claims directed to the following patentably distinct species in four genera because their structures,

functions and modes of action are different. Hence, the Examiner states that the examination of these species would require different searches in the scientific literature, which would be co-extensive. Furthermore, the Examiner states that claim 45 is generic. Applicant respectfully disagrees with the restriction of species and the identification of claim 45 as generic in the instant invention.

Applicant submits that claims 1 and 44 are both generic claims and that claim 45 limits the anti-HIV agent in claim 44. The instant invention is drawn to new and useful methods for detecting HIV, methods for assessing viral replication capacity or viral fitness, methods for detecting HIV drug resistance and susceptibility, method for designing patient customized anti-HIV drug cocktail treatments and methods for screening compositions for anti-HIV activity. In this regard, the instant invention provides novel vectors and cell lines that may the used with the above discussed methods (page 18, lines 2-7). In general, the recombinant cells used in the instantly claimed methods are (a) capable of cell division; (b) are permissive to HIV; (c) express a reporter gene whose expression is selectively regulated by the infection with HIV; and (d) allows viral replication of HIV in infected cells which enables the cells within the same culture that are initially uninfected to become infected. Since the recombinant cell become permissive to HIV by expressing cell surface receptors such as CD4, CXCR4 and CCR5, these cells are generated by transfecting the recombinant cell with a single vector comprising reporter gene and receptor genes or different vectors comprising either reporter gene or receptor genes (page 19, lines 5-15). Furthermore, since the expression level of the receptor in the recombinant cells

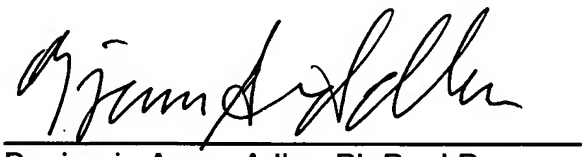
should preferably be at least 2-fold to at least 10 fold compared to the expression level in the un-transduced cells, one of skill in the art may use either PBMCs or HUT78 or any other cell line that has very low level of expression of these receptor(s). Thus, the instant specification teaches that the cell surface receptors for HIV may be expressed at an elevated level relative to the level of the corresponding cell surface receptor for HIV naturally expressed in a human cell such as human peripheral blood cell (page 19, lines 16-24). Alternatively, the recombinant cells may be produced by transducing cells that already express CD4 and one or more HIV co-receptors such as CXCR5 and CCR5 at low level with a recombinant vector containing the reporter sequence. In such cases, the cells may be HUT78 cells (page 50, line 35- page 51, line 2; page 51, line 14-21), HeLa cells (Example 1), etc. Thus, if one of skill in the art transduced a culture of PBMC with the vector, then one would expect that the tranduction would result in increased level of expression of the receptors than the parent cell, i.e. PBMCs. On the other hand, if one skilled in the art were to use cells that already express these receptors at low level, then one would such cells and compare the levels of expression with the untransduced cells. Thus, irrespective of the source of the recombinant cells, one would be able to generate a recombinant cell line that is stable, infected by multiple strains of HIV, has broad applicability, facilitates monitoring viral replication and measuring such replication, allows entry and infection in addition to efficient replication of HIV and transmission of the mature HIV virion to infect other cells.

Furthermore, with regard to the anti-HIV agent, it is known that such agents comprise inhibitors in the early stage and in the late stage of the viral replication. For instance, the early stage inhibitors may include but are not limited to entry inhibitors, reverse transcriptase inhibitors or integrase inhibitors while the late stage inhibitors may include but are not limited to protease inhibitors or virus maturation inhibitors (page 39, lines 17-25). The instant invention provides assays for detecting resistance to early stage inhibitors such as nucleotide and non-nucleotide RT inhibitors (claims 1-43; Figs. 14, 16, 17A-17C, 18A, 18B) and to late stage inhibitors such as protease inhibitors (claims 44-58; Figs. 15, 17D, 18C). Thus, one of skill in the art may use any of the methods disclosed herein based on whether the inhibitor is an early stage or a late stage inhibitor. Furthermore, with regard to the order of addition of an anti-HIV agent, Applicant submits that the order of addition of such an agent is not relevant. What matters in the instantly claimed methods is that the patient's serum and the agent are brought into contact and incubated with the recombinant cells.

In summary, a novel and inventive concept of the instant invention is generation of recombinant cell lines that overexpress CD4 and one or more co-receptors for HIV such as CXCR4 and CCR5 at high levels to render the cells susceptible to productive infection of various strains, subtypes or clades of HIV from both laboratory and clinical isolates and their use in detecting drug resistance of HIV in a sample irrespective of other factors as discussed supra. Therefore, a prior art search for the instantly claimed methods will not pose a

serious burden on the Examiner. Accordingly, based on the above-discussed reasons, Applicant respectfully requests the withdrawal of election of species for examination.

Respectfully submitted,



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